We have invited select authorities to present background information on challenging clinical problems and practical information on diagnosis and treatment for use by practitioners.

Management of Diabetes Mellitus Complicating Pregnancy

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Diabetes mellitus complicates 3–5% of all pregnancies and is a major cause of perinatal morbidity and mortality, as well as maternal morbidity. The availability of a variety of new insulins, the insulin pump, and self-monitoring of blood glucose have revolutionized the care of the pregnancy complicated by diabetes mellitus. However, challenges remain in caring for the pregnant patient with pregestational diabetes. Relatively few women receive preconceptional counseling, and major fetal malformations as a result of poor glucose control before and during the early weeks of gestation have emerged as the major cause of perinatal mortality. When the patient has diabetic vasculopathy, the obstetrician, maternal–fetal specialist, and/or endocrinologist and other members of the health care team must perform a challenging balancing act that promotes fetal health while minimizing maternal risk. As obesity increases in this country and our population becomes more diversified, the rate of gestational diabetes mellitus (GDM) will rise. Although there is controversy regarding which diagnostic standards to use for GDM, there is agreement that excellent blood glucose control, with diet and, when necessary, insulin will result in improved perinatal outcome. Finally, the goal of our educational programs should be not only to improve pregnancy outcome but also to promote healthy lifestyle changes for the mother that will last long after delivery. (Obstet Gynecol 2003;102: 857–68. © 2003 by The American College of Obstetricians and Gynecologists.)

Diabetes mellitus complicates the lives of millions of women in the United States and is observed in 3–5% of all pregnancies.[1,2] Type 2 diabetes mellitus, the most common form of diabetes mellitus in this country, is characterized by onset later in life, peripheral insulin resistance, relative insulin deficiency, obesity, and the development of vascular, renal, and neuropathic complications. The incidence of type 2 diabetes mellitus is rising rapidly, related in part to increasing obesity in the US population. More than half of the women who develop gestational diabetes mellitus (GDM), which represents approximately 90% of all cases of diabetes complicating pregnancy, will develop type 2 diabetes mellitus later in life. Type 1 diabetes mellitus occurs early in life, is characterized by an autoimmune process that destroys the insulin-producing β cells of the pancreas and therefore must be treated with insulin replacement. Like type 2 diabetes mellitus, type 1 diabetes can result in serious or even life-threatening complications. Care of the patient with type 1 diabetes mellitus, particularly in the presence of vasculopathy and nephropathy, is a significant challenge for the obstetrician and patient care team. This article will briefly review the pathophysiology of the pregnancy complicated by diabetes mellitus and will focus on a practical approach to the care of these patients.

When developing a plan of management for the patient with a medical complication of pregnancy, the obstetrician must ask two important questions. First, "How will the pregnancy affect this medical problem?" Second, "How will this medical disorder affect pregnancy outcome?" Pregnancy is characterized by increased insulin resistance and reduced sensitivity to insulin action. These changes are largely a result of the placental production of human placental lactogen and progesterone. Other hormones that may contribute include prolactin and cortisol. Early in pregnancy, relatively higher levels of estrogen enhance insulin sensitivity and, when associated with nausea and vomiting, increase the risk for maternal hypoglycemia. Insulin resistance is most marked in the third trimester. It is at

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We thank the following individuals who, in addition to members of our Editorial Board, will serve as referees for this series: Dwight P. Cruikshank, MD, Ronald S. Gibbs, MD, Gary D. V. Hankins, MD, Philip B. Mead, MD, Kenneth L. Noller, MD, Catherine Y. Spong, MD, and Edward E. Wallach, MD.

0029-7844/03/$30.00
doi:10.1016/S0029-7844(03)00810-X

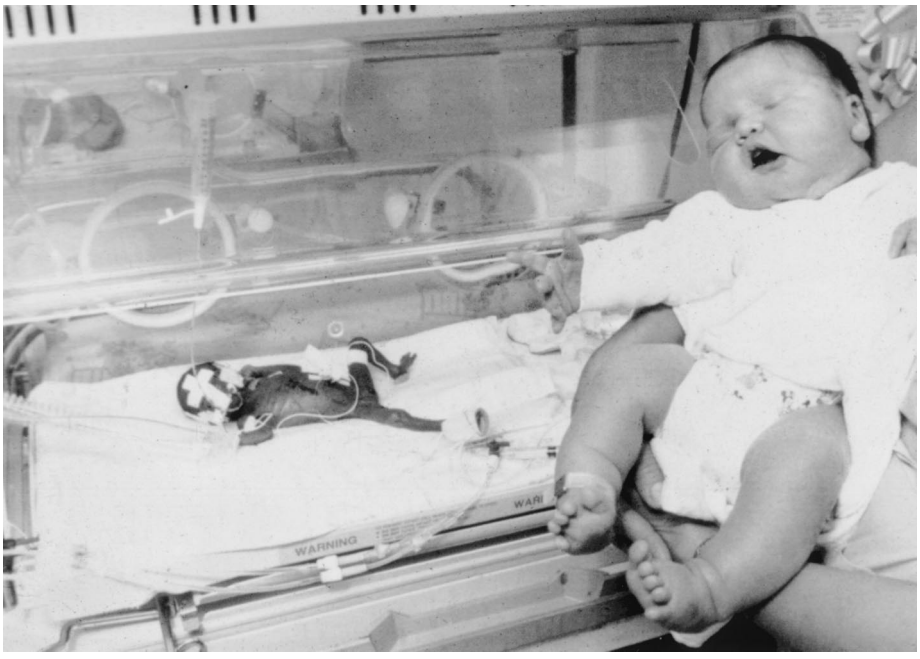

Figure 1. Two extremes of growth abnormalities seen in infants of diabetic mothers. The small growth-restricted infant on the left weighed 470 g and is the offspring of a woman with nephropathy, hypertension, and severe preeclampsia delivered at 28 weeks' gestation. The neonate on the right is the 5100-g baby of a woman with suboptimally controlled diabetes. Reprinted from Landon MB, Catalano PM, Gabbe SG. Diabetes mellitus. In: Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and problem pregnancies. Philadelphia: Churchill Livingstone, 2002:1099–100, with permission from Elsevier, Inc.

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this time that GDM most often occurs, and the risk of ketoacidosis is greatest for patients with type 1 and type 2 diabetes mellitus.

Diabetes mellitus increases the risk of important adverse outcomes of pregnancy. In women with type 1 diabetes mellitus who are poorly controlled at the time of conception and during the early weeks of gestation, the incidence of spontaneous abortion and major congenital malformations are increased.[3] Glucose crosses the placenta by facilitated diffusion and, therefore, the concentration in maternal blood determines the level in the fetus. Insulin does not cross the placenta. In the second trimester, maternal hyperglycemia produces fetal hyperglycemia, causing stimulation of the fetal β cells and fetal hyperinsulinemia. Insulin is the major fetal growth hormone and produces excessive fetal growth particularly in fat, the most insulin-sensitive tissue. The fetus of the poorly controlled diabetic mother is not only more likely to weigh more than 4000 g but to be disproportionately large about the shoulders and chest, more than doubling the risk for shoulder dystocia at vaginal delivery (Figure 1). These large fetuses are also at greater risk for intrauterine fetal death during the last 4–6 weeks of gestation.[4] Hyperinsulinemia can contribute to a significantly higher rate of respiratory distress syndrome, thwarting attempts to reduce the risk of a stillborn fetus by elective early delivery. The rate of preeclampsia is doubled in pregnancies complicated by diabetes mellitus, especially when maternal nephropathy exists. In the setting of hypertension and nephropathy, fetal growth restriction is more than doubled (Figure 1). For the infant, long-term adverse outcomes associated with intrauterine hyperglycemia and hyperinsulinemia include obesity and carbohydrate intolerance.

GESTATIONAL DIABETES MELLITUS

Gestational diabetes mellitus has been defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. The definition applies regardless of whether insulin is used for treatment or the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated the pregnancy."[5] As obesity increases in this country and our population becomes more diversified, the rate of gestational diabetes mellitus will rise. Gestational diabetes mellitus complicates 2–5% of all pregnancies and is especially common in popula-

tions with a higher rate of type 2 diabetes mellitus, such as blacks, Asian Americans, Hispanic Americans, and Native Americans.[6] Gestational diabetes mellitus is characterized in most cases by postprandial hyperglycemia, resulting from impaired insulin release and an exaggeration of the insulin resistance seen in normal pregnancies. These patients can be treated with diet therapy and have not been found to be at increased risk for intrauterine fetal death. In contrast, when fasting glucose levels are elevated, not only will insulin therapy be required, but such hyperglycemia also places these women at greater risk for a stillbirth. Although there is controversy regarding which diagnostic standards to use for GDM, there is agreement that excellent blood glucose control, with diet and, when necessary, insulin will result in an improved perinatal outcome.

The identification of women with GDM is improved by an organized screening program. Should all patients be screened for GDM? Although the US Preventive Services Task Force ". . . concludes that the evidence is insufficient to recommend for or against screening for gestational diabetes,"[7] we believe it is important for two reasons. First, identification of women with GDM, followed by appropriate treatment and monitoring, will reduce fetal macrosomia and identify those women at greater risk for fetal death. Second, given the high likelihood that women who manifest GDM will develop type 2 diabetes mellitus, identification of these patients will permit interventions after delivery that might delay or prevent the onset of type 2 diabetes mellitus. Therefore, we recommend that all pregnant women should be screened for GDM, starting with a careful history at the first prenatal visit.

The American Diabetes Association has proposed that women at low risk for GDM–that is, women who have all of the following characteristics: less than 25 years of age, normal body weight, no first-degree relative with diabetes mellitus, not a member of an ethnic group at increased risk for type 2 diabetes mellitus, no history of abnormal glucose metabolism, and no history of poor obstetric outcome–need not be screened.[8] However, the difficulty in selecting out these patients in a busy practice might make this approach impractical and, therefore, screening all women would appear to be a better choice.

For most women, glucose screening should be conducted at 24–28 weeks' gestation with use of a 50-g oral glucose load without regard to the time of day or the time of the last meal.[5] A venous plasma glucose is measured 1 hour later, and a value of 140 mg/dL or greater necessitates a full diagnostic 100-g oral glucose tolerance test (GTT). Testing at this time not only enables the obstetrician to assess glucose tolerance in the presence of the insulin-resistant state of pregnancy but, should GDM be diagnosed, permits treatment to begin before excessive fetal growth has occurred. Using a cut-off of 140 mg/dL will detect 80–90% of women with GDM and will require that a GTT be performed in 15% of patients. Lowering the cut-off to 130 mg/dL will increase the sensitivity to nearly 100% but will require GTTs in nearly 25% of all patients.[6] A value of 200 mg/dL on screening is so likely to be associated with the diagnosis of GDM that the GTT need not be performed, and treatment can be started.

Table 1. Diagnosis of GDM With Use of a 100-Gram Oral Glucose Load*

	NDDG (mg/dL)	Carpenter/Coustan conversion† (mg/dL)
Fasting	105	95
1 h	190	180
2 h	165	155
3 h	145	140

GDM = Gestational diabetes mellitus; NDDG = National Diabetes Data Group.

* Two or more of the venous plasma concentrations must be met or exceeded to establish the diagnosis of GDM.

† See reference 13.

Those women who seem to be at high risk for GDM based on their own past history of GDM, a strong family history of type 2 diabetes mellitus, or marked obesity should be tested as soon as possible.[5] If the initial screen is negative, they should be retested at 24–28 weeks' gestation. If a patient is found to have GDM before 20 weeks' gestation, she might have had diabetes mellitus antedating pregnancy. An elevated glycosylated hemoglobin level supports this and indicates that the fetus is at greater risk for major fetal malformations. Observed in approximately 2% of singleton pregnancies, glycosuria correlates poorly with blood glucose levels.[9] However, women with repetitive glycosuria should be screened for GDM.[10]

As noted above, an abnormal screening test necessitates a 100-g oral GTT, performed after an overnight fast but with the patient consuming her usual unrestricted daily diet in the days preceding the test. A fasting plasma level is first drawn, followed by samples at 1, 2, and 3 hours. If two or more values are met or exceeded, the diagnosis of GDM is established (Table 1). Most capillary glucose meters lack the precision needed for screening. If a meter is used, its precision should be known, and the relationship between simultaneously drawn venous blood samples and capillary blood samples determined.[6] Meters should not be used to diagnose GDM.[11] Two sets of cut-off values are currently in use: those proposed by the National Diabetes Data Group in 1979 and a modification of these values by Carpenter and Coustan in

1982 (Table 1).[12,13] The latter criteria have been endorsed by the American Diabetes Association.[8] Use of these lower values will increase the number of patients diagnosed with GDM from approximately 3% to 5%.[14] However, studies have demonstrated that this approach will identify women who are at comparable risk for perinatal morbidity, insulin treatment, and the subsequent development of type 2 diabetes mellitus as those seen in patients detected by the National Diabetes Data Group criteria. What should be done with patients who have a single abnormal value? Women with one abnormal value on the oral GTT demonstrate insulin resistance comparable to patients with GDM[15] and are more likely to deliver a macrosomic infant.[16] Although some have recommended that these patients be treated as though they had GDM, it is also reasonable to repeat the oral GTT in 4 weeks.

Once the diagnosis of GDM has been established, the patient should be seen every 1–2 weeks until 36 weeks' gestation and then weekly. Dietary therapy is the key element in treating patients with GDM.[17] The diet generally will consist of 2000–2200 calories per day and will emphasize the use of complex, high-fiber carbohydrates with the exclusion of concentrated sweets. The caloric prescription is based on the patient's ideal prepregnancy body weight with 30 kcal/kg for the average patient, 35 kcal/kg for the underweight patient, and 25 kcal/kg for obese women. Some have advocated diets with a caloric content as low as 1600–1800 calories for obese women in an effort to reduce weight gain and maternal hyperglycemia. If that approach is followed, the patient should be instructed to check her morning urine for ketones to determine whether the caloric content of the diet needs to be increased.[8] Patients should be encouraged to exercise at least 3 to 4 times weekly for 20–30 minutes per session. Brisk walking is ideal.

Once patients have been started on dietary therapy, it is important that capillary glucose levels be monitored to determine the efficacy of this treatment. Patients should check their fasting glucose and a 1-hour or 2-hour postprandial glucose level after each meal, for a total of four determinations each day. If, after several days of testing, it is clear that the patient is maintaining good glucose control on this regimen, the frequency of monitoring may be decreased. Should the fasting capillary glucose values be 95 or more mg/dL, the 1-hour values be 130–140 or more mg/dL, or the 2-hour values be 120 or more mg/dL, additional intervention will be required.[5] First, the patient's diet and her compliance with this regimen should be reviewed. If the patient is following her diet and if more than half of her fasting and/or postprandial values are elevated, insulin therapy should be initiated. Most women can be instructed in the use of insulin as outpatients. The starting insulin dose can be calculated based on the patient's weight; the recommended dose is 0.8 U/kg actual body weight per day in the first trimester, 1.0 U/kg per day in the second trimester, and 1.2 U/kg per day in the third trimester.[18] The total dose is divided, with two-thirds administered in the fasting state as two-thirds NPH and one-third rapid-acting insulin, and the remaining one-third of the total dose given as one-half rapid acting insulin at dinner and one-half at bedtime as NPH. Regular insulin or insulin lispro may be used. Appropriate increases in insulin dosage are made on the basis of monitoring not only fasting glucose but also levels before and after each meal and at bedtime.

An alternative to insulin therapy is the oral hypoglycemic agent glyburide. This second-generation sulphonylurea does not cross the placenta. It has its onset of action in approximately 4 hours and has a duration of action of approximately 10 hours. In a study of 404 women conducted by Langer et al,[19] glyburide was found to be comparable to insulin in improving glucose control, with less than 10% of patients randomized to glyburide requiring insulin. Although there was no difference noted in maternal complications or neonatal outcomes, the rate of maternal hypoglycemia was significantly lower with glyburide. In our experience, glyburide has become the first choice of our patients with GDM who require therapy beyond diet. We begin with a starting dose of 2.5 mg twice daily and increase the dose as necessary. Most patients will require, on average, 5 mg twice daily. The maximum dose is 10 mg twice daily. Certainly, additional studies of glyburide therapy in a larger and more diverse patient population are needed.

Patients with GDM treated with diet are followed until 40 to 41 weeks' gestation. At 40 weeks' gestation, they are begun on a program of fetal assessment with twice weekly nonstress tests (NSTs).[20] Patients with GDM who have had a previous stillborn fetus or have hypertension are started on twice-weekly NSTs at 32 weeks' gestation. Clinical estimation of fetal size and ultrasonography are used to detect fetal macrosomia, most often reflected as accelerated growth of the fetal abdominal circumference. If the fetal weight is estimated to be 4500 g or more, cesarean delivery should be considered to reduce the risk of shoulder dystocia. Of course, the patient's past obstetric history and clinical pelvimetry are used when counseling the patient as to the route of delivery.[6] Patients who require insulin or glyburide as well as diet to maintain normoglycemia are followed with a program of antepartum fetal surveillance identical to that used for women with pregestational diabetes, that is, twice-weekly NSTs. If well-controlled, these patients may be allowed to progress to their due date. In poorly controlled patients, an elective delivery may be consid-

Table 2. Evaluation for Postpartum Carbohydrate Intolerance

Normal	Impaired fasting glucose or impaired glucose tolerance	Diabetes mellitus
Fasting < 110 mg/dL	110–125 mg/dL	≥ 126 mg/dL
2 h < 140 mg/dL*	2h ≥ 140–199 mg/dL*	2h ≥ 200 mg/dL*

* Requires a 75-g oral glucose load.

ered at 38 to 39 weeks' gestation. If delivery is scheduled before 39 weeks' gestation, an amniocentesis to assess fetal lung maturity is performed. While in labor, patients with GDM who have been treated with insulin or glyburide should have their capillary glucose levels checked at the bedside every 1 to 2 hours. They will rarely require insulin therapy to maintain a glucose level of no more than 110 mg/dL. After birth, the infant of a patient with GDM should be observed closely for hypoglycemia, hypocalcemia, and hyperbilirubinemia. Breast-feeding should be encouraged.

It is essential that the patient be evaluated postpartum to determine whether she has returned to a state of normal carbohydrate tolerance. Women who are diagnosed with GDM early in gestation who are obese and have required insulin or glyburide therapy are most likely to demonstrate persistent glucose intolerance or diabetes mellitus.[21] Approximately 15% of women who have had GDM will remain glucose intolerant or will demonstrate overt diabetes in the postpartum state. The American Diabetes Association recommends that a 75-g oral GTT administered under the conditions described for the 100-g oral GTT be performed 6–8 weeks after delivery (Table 2).[8] Patients may also continue to monitor their fasting and postprandial glucose levels. If these remain normal during the first 6 weeks postpartum, it is unlikely that the patient will have an abnormal GTT. If the patient's postpartum GTT is normal, she should be evaluated at no less than 3-year intervals with a fasting glucose. Should the patient have glucose intolerance documented in the postpartum period, she should be managed with dietary treatment and exercise and be followed annually. All patients who have had GDM should be encouraged to exercise and lose weight if they are obese, to reduce the likelihood of their developing type 2 diabetes mellitus.[22] They should be evaluated for glucose intolerance or diabetes mellitus before a subsequent pregnancy and treated if necessary to decrease the likelihood of their having an infant with a major congenital malformation. Patients who have had GDM may use combination low-dose estrogen and progestogen oral contraceptives for family planning without concerns that these medications will cause deterioration of carbohydrate tolerance.

Table 3. Congenital Malformations in Infants of Diabetic Mothers

Cardiovascular
Atrial septal defect
Ventricular septal defect
Hypoplastic left heart
Transposition of the great vessels
Tetralogy of Fallot
Truncus arteriosis
Central nervous system
Anencephaly
Encephalocele
Meningomyelocele
Holoprosencephaly
Skeletal
Sacral agenesis
Genitourinary
Renal agenesis
Polycystic kidneys

TYPE 1 AND TYPE 2 DIABETES MELLITUS

Preconceptional Counseling

Major congenital anomalies are the leading cause of perinatal mortality in pregnancies complicated by diabetes mellitus, occurring in 6–12% of all infants.[3] Molsted-Pederson et al[23] examined 835 consecutive infants of diabetic mothers and compared them with 1212 infants of nondiabetic mothers. Fatal malformations and malformations involving more than one organ system were six times more frequent in the infants of diabetic mothers. Poor glucose control during the critical weeks of organogenesis, 5–8 weeks after the last menstrual period, is thought to be the key etiologic factor.[3] The glycosylated hemoglobin level, which reflects average glucose control over the past 2 to 3 months, can be closely correlated with the frequency of anomalies. Miller et al[24] demonstrated that when the glycosylated hemoglobin levels were no more than 8.5%, the fetal malformation rate was 3.4%. However, when the glycosylated hemoglobin was greater than 9.5%, the rate of fetal malformations approached 22%. Complex cardiac defects, central nervous system anomalies, such as anencephaly and spina bifida, and skeletal malformations, including sacral agenesis, are most common (Table 3, Figure 2).[23] Studies have also linked an increased rate of spontaneous abortion to poor preconception control.[25] Most major anomalies can be detected by a targeted ultrasound, which includes a carefully performed assessment of fetal cardiac structure, including the great vessels at 18–20 weeks' gestation.[26]

Both major malformations and spontaneous abortion can be reduced when excellent prepregnancy and early

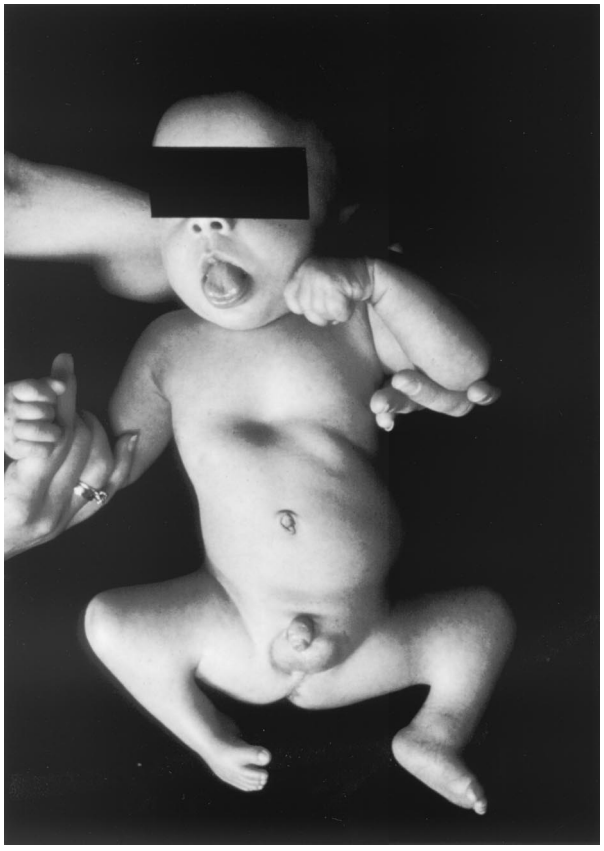

Figure 2. Infant of a diabetic mother with sacral agenesis (caudal regression syndrome). The mother of this infant presented for her first prenatal visit at 26 weeks' gestation with previously undiagnosed nephropathy and poor glycemic control. Ultrasound examination revealed absent lower lumbar spine and sacrum and hypoplastic lower extremities. Reprinted from Landon MB, Catalano PM, Gabbe SG. Diabetes mellitus. In: Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and problem pregnancies. Philadelphia: Churchill Livingstone, 2002:1099–100, with permission from Elsevier, Inc.

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postconceptional diabetic control are achieved. It is, therefore, imperative that patients with diabetes mellitus be encouraged to seek preconceptional care. However, in the United States, less than one third of women with diabetes mellitus receive preconceptional counseling. For a woman with diabetes mellitus, any visit to a health care provider should be used as an opportunity to review the patient's plans for pregnancy. The discussion should focus on obtaining excellent glucose control and achieving a healthy lifestyle before conception. Glucose levels should be stabilized and a glycosylated hemoglobin level less than 1% above the normal range achieved.[27] Angiotensin-converting enzyme inhibitors should be discontinued, and, because they will invariably require insulin when pregnant, patients with type 2 diabetes who are using oral agents should be converted to insulin. In addition, an evaluation for vasculopathy should be accomplished. Family planning should also be discussed.[2] Low-dose combination oral contraceptives may be used in women without vasculopathy, whereas progestin-only pills can be prescribed for women with vascular disease. Barrier methods, although less effective, will not affect glucose control or vascular disease. The intrauterine device can be used by multiparous women with a monogamous relationship. Sterilization should be considered for women with serious vasculopathy or for those who have completed their families.

Retinopathy

Diabetic retinopathy, the leading cause of blindness in patients between 24 and 64 years of age, includes a wide spectrum of lesions: background retinopathy, including retinal microaneurysms and dot–blot hemorrhages; preproliferative changes, including cotton wool infarcts; and proliferative retinopathy with marked neovascularization. The presence and the severity of retinopathy can be attributed to poor glycemic control. The rapid institution of strict glycemic control during pregnancy has been associated with short-term progression of retinopathy. Worsening of retinopathy is also more likely to occur in hypertensive patients.[28] Few long-term studies have examined the effect of pregnancy on retinopathy. However, two reports have shown no difference in retinopathy between parous and nulliparous women.[29,30] These findings suggest that although pregnancy might accelerate the short-term progression of retinopathy, it has no long-term effect on the disease process. Active proliferative retinopathy might worsen in pregnancy and should ideally be controlled with laser therapy before conception.

All patients should be scheduled for screening retinal examinations at their first prenatal visit. If retinopathy is present, then follow-up examinations during the pregnancy and postpartum are recommended.

Nephropathy

Diabetic nephropathy will eventually appear in 30–40% of patients with type 1 diabetes and is the most common cause of end-stage renal disease in the United States. The prevalence during pregnancy has been estimated to range from 5% to 10%.[31] Pregnancies complicated by nephropathy are at increased risk for maternal and fetal morbidity and perinatal morality. Diabetic nephropathy significantly increases the risk of maternal hypertensive complications, including preeclampsia, preterm birth because of worsening maternal disease, and fetal growth restriction. Renal dysfunction as measured by decreased creatinine clearance and proteinuria is the best predictors

of poor perinatal outcome. Although proteinuria will increase during gestation, most studies have failed to demonstrate a permanent worsening in pregnancy. However, in a small subset of women with advanced renal disease, those with a serum creatinine exceeding 1.5 mg/dL, pregnancy might accelerate progression to end-stage renal disease.[31] All patients with a history of microalbuminuria or those with diabetes of greater than 10 years' duration should be screened with a 24-hour urine collection for total protein and creatinine before pregnancy or at the initial prenatal visit.

Coronary Artery Disease

Women with diabetes mellitus are at increased risk for coronary artery disease. Patients with long-standing disease who have developed hypertension and nephropathy are at the highest risk.[32] The hemodynamic changes associated with pregnancy increase myocardial stress. Furthermore, epinephrine released in response to hypoglycemia might exacerbate the risk for myocardial injury. Coronary artery disease is a potential contraindication to pregnancy. These patients should undergo preconception counseling and be informed of these risks before attempting pregnancy. Baseline studies, including an electrocardiogram and echocardiography, should be considered.

Other Maternal Complications

Diabetic neuropathy, either peripheral or autonomic, has not been well studied in pregnancy. However, nausea and vomiting commonly seen during pregnancy might be worsened in patients with gastroparesis.[33] Peripheral neuropathy should be assessed at the preconception visit or early in gestation by a careful examination of the patient's feet for sensory loss. Instructions on safe foot care should be provided for all women with diabetes.

Management

The management of diabetes in pregnancy includes a careful combination of diet, exercise, and insulin therapy. During pregnancy in patients with a singleton fetus, caloric requirements are increased approximately 300 kcal above basal needs.[17] New guidelines advocate the use of carbohydrate counting to increase dietary flexibility. Carbohydrate counting is extremely useful in pregnancy, so long as one considers overall daily caloric intake to avoid excessive weight gain. For women with a normal body weight, the diet is usually 30–35 kcal/kg of actual weight, with an increase to 30–40 kcal/kg in women who are less than 90% of desirable body weight and 24 kcal/kg in those who are more than 120% of desirable body weight. Caloric composition includes 40–50% from complex, high-fiber carbohydrates, 20% from protein, and 30–40% from primarily unsaturated fats. The calories may be distributed 10–20% at breakfast, 20–30% at lunch, 30–40% at dinner, and 30% with snacks, especially a bedtime snack to reduce nocturnal hypoglycemia.

Table 4. Action Profile of Commonly Used Insulins

Insulin	Onset of action	Peak of action (h)	Duration of action (h)
Lispro	1–15 min	1–2	4–5
Regular	30–60 min	2–4	6–8
NPH	1–3 h	5–7	13–18
Lente	1–3 h	4–8	13–20
Ultralente	2–4 h	8–14	18–30
Glargine	1 h	No peak	24

In the women with pregestational diabetes, insulin is the mainstay of therapy. Metformin has been used as a treatment for infertility in polycystic ovary disease. Although metformin is a category B drug, its use in pregnancy has not been well studied, and it is has been recommended that the drug be stopped once pregnancy has been established.[34,35]

Today, most insulin used in the treatment of diabetes is biosynthetic human insulin. Insulin requirements will increase throughout pregnancy, most markedly in the period between 28 and 32 weeks' gestation. As noted above, insulin needs rise from 0.8 units/kg body weight per day in the first trimester, to 1.0 units/kg per day in the second trimester, and 1.2 units/kg per day in the third trimester.[18] Maintaining capillary glucose levels as close to normal as possible is the goal of therapy, including a fasting glucose level of no more than 95 mg/dL, premeal values of no more than 100 mg/dL, 1-hour postprandial levels of no more than 140 mg/dL, and 2-hour postprandial values of no more than 120 mg/dL.[36] During the night, glucose levels should not fall below 60 mg/dL. Mean capillary glucose levels should be maintained at an average of 100 mg/dL, with a glycosylated hemoglobin level no higher than 6%. The ability to achieve physiologic glucose control will depend on the patient's motivation, her ability to understand the complex interactions between diet, insulin, and exercise, the support she receives from the health care team, including the obstetrician or maternal–fetal medicine specialist, nutritionist, and teaching nurse, and her ability to recognize hypoglycemia.

Short- or rapid-acting insulins (prandial insulins) are administered before meals to reduce glucose elevations associated with eating and allow utilization of consumed fuels.[37,38] Longer-acting insulins are basal insulins, used to restrain hepatic glucose production between meals and in the fasting state (Table 4). The two most commonly used rapid-acting insulins are regular and insulin lispro. Although, insulin lispro may be used in place of

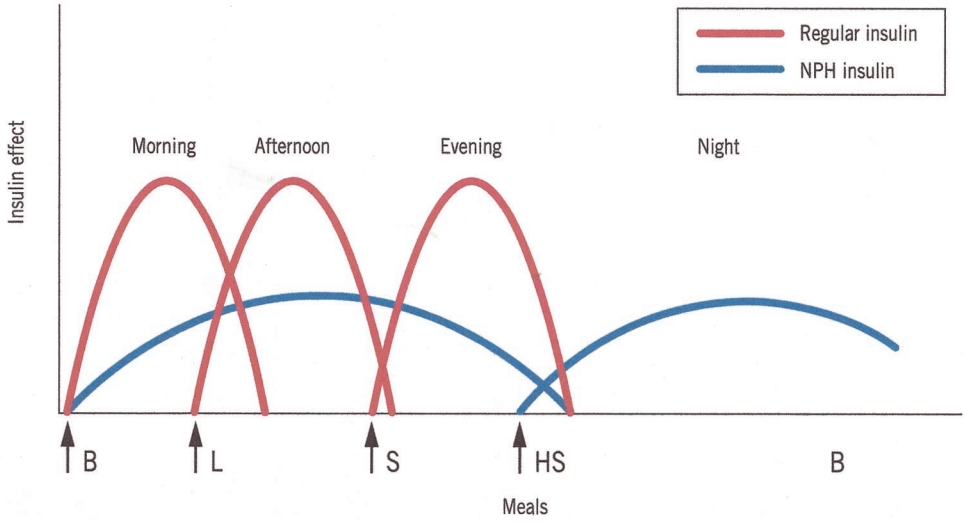

Figure 3. A combination of rapid-acting and longer-acting insulins (in this illustration, regular [REG] insulin and NPH, respectively) is used to control maternal glucose levels. An injection of regular insulin is used with each meal. Insulin lispro may also be substituted. NPH insulin is administered to control glucose levels in the basal state between meals. The NPH dose in the morning is usually larger because this period of the day is associated with greater insulin resistance. Administration of the second injection of NPH at bedtime delays its peak effect until early morning and reduces the risk for nocturnal hypoglycemia. B = breakfast; L = lunch; S = supper; HS = bedtime.

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regular insulin, they are not interchangeable. Regular insulin has its peak effect at 2 to 3 hours with a long duration of action, 4–6 hours, giving it features of a basal insulin. Regular insulin should be administered approximately 30 minutes before eating. Insulin lispro has its peak effect in 1 to 2 hours with a duration of 4 hours. Because of its rapid onset of action, 15–20 minutes, it should be given immediately before eating. Although its rapid onset of action improves compliance, insulin lispro can cause significant hypoglycemia in the unprepared patient. It is also more expensive than regular insulin. Bhattacharyya et al[39] noted that patients who were treated with insulin lispro had lower predelivery glycosylated hemoglobin levels and a higher level of patient satisfaction.[39] There has been some concern regarding the progression of diabetic retinopathy in patients who use insulin lispro. However, this has not been supported by recent studies.[40]

Intermediate-acting insulin (NPH or Lente) has its peak effect in approximately 8 hours, with a duration of about 12–24 hours. This insulin is usually given before breakfast with a short-acting insulin and before the evening meal or at bedtime (Figure 3). Bedtime dosing is preferred because an injection given with the evening meal might increase the risks of nocturnal hypoglycemia. Long-acting insulins include ultralente and glargine. Ultralente has an onset of action of 1 to 2 hours, with a peak at approximately 16–18 hours and may be administered once or twice daily. Its prolonged duration of action might make it difficult to determine the timing of its effect, especially if it is given twice daily. Glargine is a recently developed human insulin analog produced with recombinant deoxyribonucleic acid by the addition of two arginines to the C-terminus of the insulin β chain and replacement of asparagine with glycine at position 21 of the insulin α chain.[41] This alteration delays insulin absorption and creates a truly basal insulin with no peak and a 24-hour duration. Experience with glargine in pregnancy has been limited.

In patients who are highly insulin resistant, regular U-500 (concentrated) insulin might be valuable. Although it has a rapid onset, its duration of action is more like that of an intermediate-acting insulin. Regular U-500 insulin is recommended for those patients who require more than 200 units of insulin per day. It can be given in three equally divided doses before breakfast, lunch, and dinner in conjunction with a dose of NPH at bedtime. That regular U-500 is five times more concentrated than regular insulin must be emphasized to the patient.

Continuous subcutaneous insulin infusion therapy–the insulin pump–is used to deliver insulin in a pattern that closely resembles physiologic insulin secretion.[37] A short-acting insulin, most often regular or insulin lispro, is used. Usually 50–60% of the total daily dose is administered as a continuous basal rate, with boluses before meals and snacks making up 40–50% of the total daily

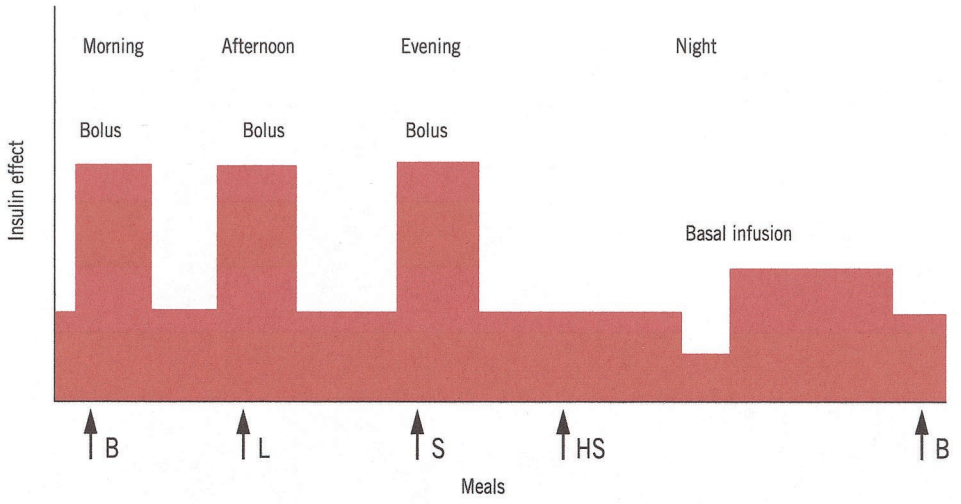

Figure 4. Profile of insulin administration in a patient using an insulin pump. The basal infusion is maintained at a constant rate during most of the day but is lowered late in the evening and in the hours after midnight to reduce the risk of nocturnal hypoglycemia. The basal infusion rate is increased in the early morning hours in response to the "dawn phenomenon," which heightens insulin resistance. Boluses are administered with meals or snacks. B = breakfast; L = lunch; S = supper; HS = bedtime.

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dose (Figure 4). Patients who use an insulin pump must be highly motivated and compliant. The advantages of the pump include a more flexible lifestyle (making it ideal for physicians and nurses with diabetes), improved patient satisfaction, a decrease in severe hypoglycemia, and better control of early morning hyperglycemia due to the "dawn phenomenon."[42] Major disadvantages include the increased cost of the pump itself and pump supplies. In addition, should the administration of insulin be interrupted or impaired by a battery failure or infection at

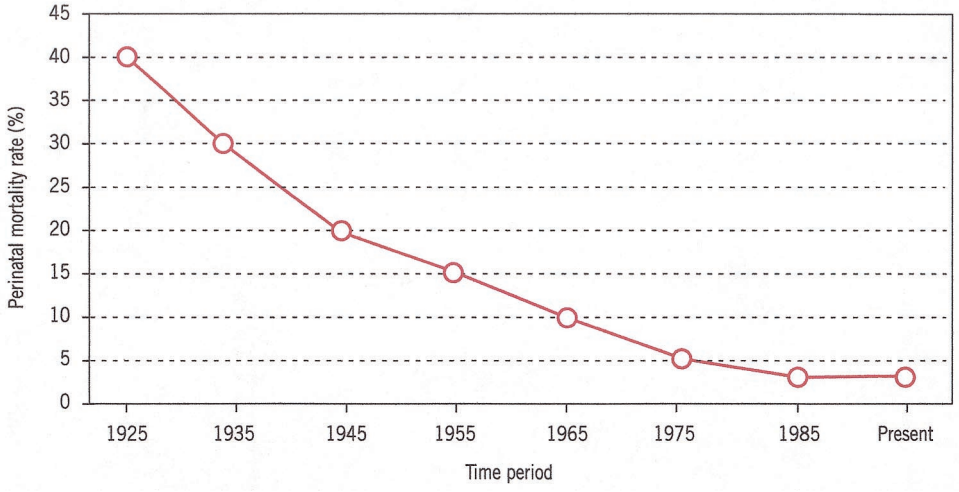

Figure 5. Perinatal mortality rate in pregnancies complicated by type 1 diabetes mellitus. Perinatal deaths have declined dramatically since the discovery of insulin in 1921, a result of improved control of maternal glucose levels, advances in neonatal care, and reliable techniques for antepartum fetal monitoring, which have allowed safe prolongation of gestation and delivery at term. Reprinted from Landon MB, Catalano PM, Gabbe SG. Diabetes mellitus. In: Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and problem pregnancies. Philadelphia: Churchill Livingstone, 2002:1099–100, with permission from Elsevier Inc.

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the infusion site, diabetic ketoacidosis might develop rapidly. A recent study has noted that women who initiate pump therapy during pregnancy are highly likely to continue with the pump after they deliver. They maintain better glucose control than do patients remaining on multiple insulin injections.[42]

Frequent capillary blood glucose monitoring is imperative to achieve euglycemia without significant hypoglycemia during pregnancy. A glucose meter with a memory should be used to check capillary glucose levels in the fasting state, before and after each meal, and before bedtime. Insulin and diet should be adjusted in response to trends of hyper- or hypoglycemia. In selected patients, especially those using insulin pumps, determinations at 2:00 to 3:00 AM might help detect nocturnal hypoglycemia or pump failure. In general, insulin doses are changed plus or minus 20% in response to this information. It is also helpful to provide general guidelines on insulin use and carbohydrate intake; for example, 1) for most patients, 1 unit of rapid-acting insulin will lower blood glucose 30 mg/dl, 2) 10 g of carbohydrate will elevate blood glucose 30 mg/dL, and 3) one unit of rapid-acting insulin will cover consumption of 10 g of carbohydrate. A glycosylated hemoglobin test in each trimester will provide an overview of glucose control.

Even with meticulous monitoring, hypoglycemia is more frequent in pregnancy. Rosenn et al[43] reported an incidence of 71% for moderate hypoglycemia requiring assistance and 34% for severe hypoglycemia with loss of consciousness. Intensively treated pregnant women with type 1 diabetes mellitus seem to have impaired counterregulatory responses to hypoglycemia, with diminished release of epinephrine and glucagon.[44] Maternal glucose levels drop more rapidly overnight owing to placental and fetal glucose consumption while the mother is fasting. This "accelerated starvation" might further increase the risk for nocturnal hypoglycemia. In response to hypoglycemia, the patient and her health care team should carefully review her diet, insulin regimen, and exercise program. The patient and her family must be taught how to respond appropriately to hypoglycemia (eg, with a glass of milk for moderate hypoglycemia and glucagon for severe cases).

Antepartum Management

Antepartum fetal assessment has proved to be a valuable approach to safely prolonging the pregnancies of women with type 1 and type 2 diabetes. The NST has become the most widely applied technique. In 1981, Barrett et al[45] reported a stillborn fetus rate of 4% in patients with a reactive NST within 1 week of delivery. In response to this study, twice weekly testing has been widely adopted. More recently, a biophysical profile (BPP) score of 8 out of 10 has been shown to be as reliable as a reactive NST in predicting fetal well-being. Daily fetal movement counting is a simple technique for antepartum assessment that should also be considered. In our institution, patients with type 1 and type 2 diabetes are monitored twice weekly with an alternating BPP and NST beginning at 32 weeks' gestation. Doppler velocimetry of the umbilical artery might be useful in monitoring pregnancies with vascular complications and poor fetal growth.[46]

The likelihood for an abnormal test is increased in patients who have had poor glucose control or have vasculopathy with a growth-restricted fetus. Should there be a combination of abnormal test results, such as decreased fetal movement, a nonreactive NST, and an abnormal BPP or contraction stress test, delivery should be considered. In a preterm gestation, an amniocentesis to assess fetal lung maturity might help in the decision-making process. In this setting, if corticosteroids are administered to accelerate lung maturation, an increased insulin requirement over the next 5 days should be anticipated, and the patient's glucose levels must be closely monitored.[47]

Optimal timing of delivery relies on carefully balancing the risks of intrauterine fetal death and excessive fetal growth if pregnancy is continued versus the risks of prematurity. If delivery is to be performed before 39 weeks' gestation, an amniocentesis is recommended to assess fetal lung maturity. The obstetrician should be familiar with the test used in his or her institution and how it has performed in the pregnancy complicated by diabetes, because falsely mature tests might be more frequent. Well-controlled patients may be allowed to progress to their expected date of delivery with reassuring twice-weekly testing. To prevent traumatic birth injury, it is recommended that cesarean delivery be considered if the estimated fetal weight is greater than 4500 g. During induction of labor, maternal glycemia can be controlled with an intravenous infusion of regular insulin titrated to maintain hourly readings of capillary blood glucose of less than 110 mg/dL. Avoiding maternal hyperglycemia intrapartum will prevent fetal hyperglycemia and reduce the likelihood of subsequent neonatal hypoglycemia.

Insulin requirements decrease rapidly after delivery. One half of the predelivery dose may be reinstituted before starting regular food intake.[36] For patients delivered by cesarean, rapid-acting insulin may be used to treat glucose values greater than 140–150 mg/dL, until a regular meal pattern has been established. Breast-feeding should be encouraged in women with type 1 and type 2 diabetes mellitus.

SUMMARY

Diabetes mellitus is one of the most common medical complications of pregnancy, affecting more than 200,000 women in the United States each year. Gestational diabetes mellitus represents approximately 90% of these cases and results from heightened insulin resistance during gestation. The detection of GDM requires a carefully developed plan for screening. Most women with GDM will respond to dietary therapy. The greatest perinatal risk in such cases is fetal macrosomia, which has been associated with a higher rate of cesarean delivery. Women with GDM are at considerable risk for the development of type 2 diabetes mellitus later in life and will require careful follow-up. Women with type 1 and type 2 diabetes mellitus are at greater risk for maternal morbidity and perinatal morbidity and mortality (Figure 5). These risks are greatest in those women who have poor glucose control and vasculopathy. When the patient has diabetic vasculopathy, the obstetrician, maternal–fetal specialist, and/or endocrinologist and other members of the health care team must perform a challenging balancing act that promotes fetal health while minimizing maternal risk. The leading cause of perinatal mortality in pregnancies complicated by type 1 and type 2 diabetes mellitus is the major congenital malformation. These anomalies can be prevented by excellent control of maternal glycemia before gestation and during the early weeks of pregnancy. Today, women with diabetes mellitus who receive excellent medical care can look forward to a pregnancy outcome that approaches that of women without diabetes mellitus. Finally, the goal of our educational programs should be not only to improve pregnancy outcome but also to promote healthy lifestyle changes for the mother that will last long after delivery.

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Received May 21, 2003. Received in revised form July 2, 2003. Accepted July 10, 2003.